Diabetic Foot Ulcer Management and Predictive Markers for Using Advanced Therapies

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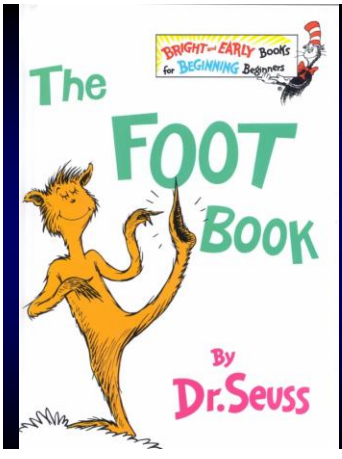
Objectives

- To discuss the epidemiology of the diabetic foot
- To learn about the pathophysiology of diabetic foot ulcer formation
- To review predictive markers when considering advanced therapies
- To learn about vascular disease and the angiosome concept in the diabetic foot
- To discuss interesting cases



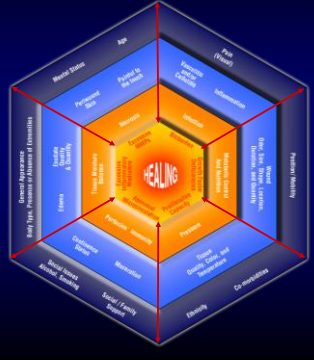
"Think like an internist, before you act like a surgeon" Wm. Ennis, DO

- **Wound management often requires a subtle balance between medical and surgical interventions.**

Sometimes Clinicians Become Confused

Core Healing Principles

- Patient factors
- Physical aspects
- MACROscopic environment
- MICROscopic environment



Wound specialists have to be medical detectives

Wound Etiology

Mechanical
Arterial
Venous
Neuropathic
Malignancy
Vasculitic
Other

(Courtesy of Sharon Baranoski, RN)

Address the etiology




Don't get caught with your pants down!

Acute Wounds

Examples

- Lacerations
- Abrasions
- Punctures
- Burns
- Surgical Incisions

Characteristics

- Heal in an expected time frame
- Cause is transient
- Usually lack significant impediments to healing
- Repair is sustained

Chronic Wounds/Ulcers

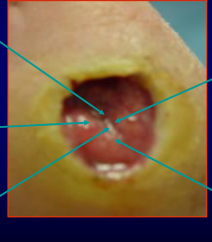
Examples

- Pressure ulcers
- Diabetic neuropathic ulcers
- Venous Insufficiency ulcers
- Arterial Insufficiency ulcers
- Inflammatory ulcers

Characteristics

- Non-healing, slow healing
- Cause is ongoing
- Multiple systemic and local impediments to healing
- Wound often recurs

Proposed Mechanisms for Chronicity in Diabetic Foot Ulcer (Kirsner et al)



Unresponsive and/or Senescent Cells

Non migratory, hyperproliferative edge epithelium

Proteolytic/ Inflammatory environment

Deficient and/or unavailable growth factors/receptor sites

Bacterial interference

Incidence of Common Chronic Wounds

Diabetic Neuropathic Ulcers	*> 340,000/yr*
Venous Stasis Ulcers	*> 500,000/yr*
Pressure Ulcers	***>** 2.1 million/yr*

Impact of Diabetes

- **1.3 million new cases (incident cases) of diabetes are diagnosed annually in the US in people aged 20 and over[1]**
- **Prevalence of total diabetes in the US for all ages was 6.3%-7%**
- **Economic burden of diabetes**
  - **Patients with diabetes in a Medicare population incur 1.7 times the health care expenditures of those without diabetes[2]**
  - **Diabetic employees within a private health insurance group incur higher mean annual costs than their non-diabetic counterparts ($7,778 vs $3,367)[3]**

1. Centers for Disease Control 2003
2. Krop 1999
3. Ramsey 2002

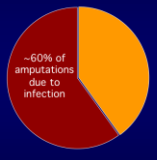
Diabetic Foot Ulcers

- **One of the most common complications of diabetes**
- **Annual incidence**
- **Lifeti**
- **~**
- **~85**
- **Peripheral neuropathy is a major contributing factor in diabetic foot ulcers[1-7]**
  - **Other factors: foot deformity, callus, trauma, infection, and peripheral vascular disease**

1 million amputations globally in patients with diabetes (every 30 seconds)
In the US; 1200 amputations weekly

1. Reiber and Ledoux. In *The Evidence Base for Diabetes Care*. Williams et al, eds. Hoboken, NJ: John Wiley & Sons; 2002:641–665.
2. Boulton et al. *NEJM*. 2004;351:48.
3. Sanders. *J Am Podiatry Med Assoc*. 1994;84:322.
4. Boulton et al. *Lancet*. 2005;366:1719.
5. Ramsey et al. *Diabetes Care* 1999;22:382.
6. Pecoraro et al. *Diabetes Care*. 1990;13:513.
7. Apelqvist and Larsson. *Diabetes Metab Res Rev*. 2000;16:S75.

Infection Contributes to Various Complications Including Amputation



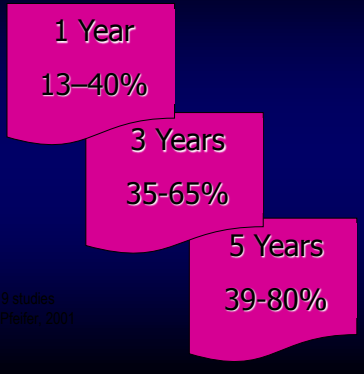
Infection plays a role in about 60% of the DFU cases that result in amputation

- **Risk factors for infection:**
  - **Wounds that penetrate to the bone**
  - **Wounds with a duration > 30 days**
  - **Recurrent foot wounds**
  - **Wounds with a traumatic**

Peripheral vascular disease
Pain
Deterioration of the wound
Foul odor

DFU = diabetic foot ulcer.
Lipsky. *Diabetes Metab Res Rev*. 2004;24:S66.
Lavery, Armstrong, et al. *Diabetes Care*. 2006;29:1288.

Post-op Mortality Rates Among Diabetic Amputees



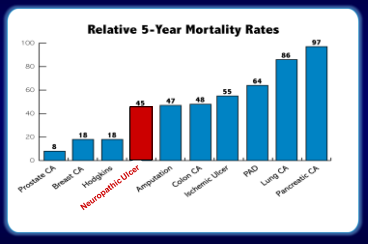
Data from 9 studies
Bowker & Pfeifer. 2001

Diabetic Ulcers

- Once amputation occurs:
  50% of patients develop an ulcer in the contra-lateral limb within 18 months of the amputation

Reiber, Boyko, Smith. Lower-extremity foot ulcers and amputations in diabetes. In: *Diabetes in America, Second Edition*. Bethesda, MD: National Institutes of Health, 1995:409-28. NIH Publication No. 95-1468.

Consequences of Unhealed Neuropathic Ulcers



- Nearly half of all unhealed neuropathic ulcers result in death within 5 years

Armstrong DG. *Int Wound J.* 2007;4(4):286-287.

History of Foot Ulcer Increases Mortality Among Individuals with Diabetes

Ten Year Follow-up of the Nord-Trøndelag Health Study, Norway

- A large population based study examined the association between foot ulcers in patients with diabetes and mortality risk while controlling for disease factors
- Foot ulcers were independently associated with increased mortality risk
  - Patients with diabetes and a foot ulcer had an increased mortality risk of 2.3-fold (229%) compared to non-diabetic subjects
  - In patients with diabetes, presence of a foot ulcer alone increased mortality risk by 47%

Population	Mortality Rate	Hazard Risk; Db+HFU vs. Non-Db	Hazard Risk; Db+HFU vs. Db-HFU
Non-Db (N=63,632)	10.5%		
Db+HFU (N=155)	49.0%	2.29 [95% CI 1.82–2.88]	1.47 [95% CI 1.14–1.89]
Db-HFU (N=1339)	35.2%		

Db = Diabetic; HFU = history of foot ulcer
Hazard risk calculated via Cox regression analyses, adjusted for demographic and lifestyle factors

Iversen et al. Diabetes Care. 2009;32:2193-9.

Just having a neuropathic foot ulcer is a marker for death!

Snyder RJ(2010) Podiatry Management

Sometimes it is hard to get ahead of the curve

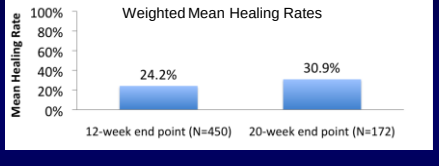
The extent of the problem of "problem wounds"…Diabetic Foot Ulcers

- In Denmark a multidisciplinary wound management program integrating vascular intervention and wound care has reduced LEA rate by 75%

Gottrupp, F, et al. Arch Surg 2001; 136: 765-772
Holstein P. Diabetologia 2000; 43: 844-847.

Sen C, et al Human skin wounds: A major and snowballing threat to public health and the economy. WRR 2009: 17(6):763-771

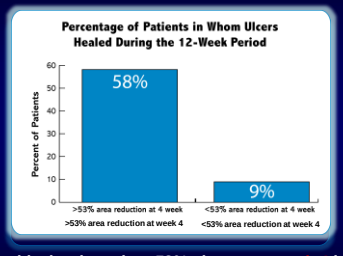
Healing Neuropathic Ulcers: Results of a Meta-analysis



- These data provide clinicians with a realistic assessment of their chances of healing neuropathic ulcers
- Even with good, standard wound care, healing neuropathic ulcers in patients with diabetes continues to be a challenge

Margolis et al. *Diabetes Care.*

Continuing Research: Healing of Diabetic Foot Ulcers After 4 Weeks



- **Wounds achieving less than 53% closure at week 4 have minimal chance of healing with conventional therapy**

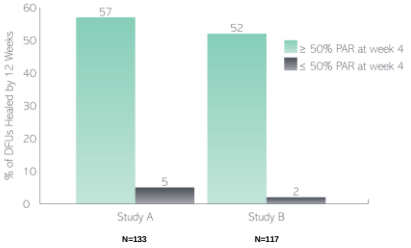
Sheehan et al. *Diabetes Care*. 2003;26(6):1879-1882.

Post- hoc Analysis

A Post-hoc Analysis of Reduction in Diabetic Foot Ulcer Size at 4 Weeks as a Predictor of Healing by 12 Weeks

Robert J. Snyder, DPM, CWS; Matthew Cardinal, MS; Damien M. Dauphinée, DPM, FACFAS, CWS; and James Stavosky, DPM

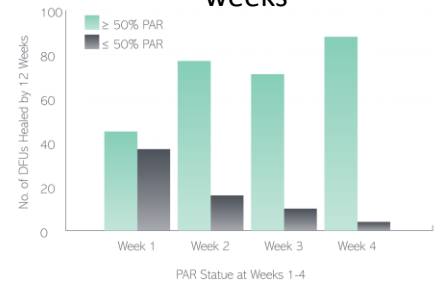
Association Between PAR at Week 4 & DFU Closure at Week 12



- Data was dichotomized by PAR of <50% or ≥ 50% by week 4 to assess the association of PAR with DFU closure by 12 weeks

Snyder RJ, et al. Ostomy Wound Management. 2010

Number of DFUs that healed by 12 weeks



- Results suggest that PAR at week 4 is the best prognostic indicator of healing by 12 weeks because it provides the highest specificity and sensitivity

ORIGINAL ARTICLE

Differentiating diabetic foot ulcers that are unlikely to heal by 12 weeks following achieving 50% percent area reduction at 4 weeks

Robert A Warriner, Robert J Snyder, Matthew H Cardinal

Warriner RA, Snyder RJ, Cardinal MH. Differentiating diabetic foot ulcers that are unlikely to heal by 12 weeks following achieving 50% percent area reduction at 4 weeks. Int Wound J 2011; 8:632–637

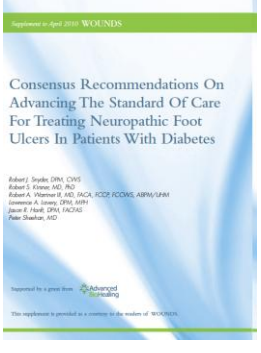
ABSTRACT

This retrospective analysis incl… …ized, randomised, diabetic foot ulcer (DFU… …dy healing progre… th… D… heali… ≥90% versu… <90% at 8 weeks provide…

Ulcers that fail to progress or worsen from weeks 4 to 6 and those that fail to achieve 90% PAR at week 8 are unlikely to heal by week 12

Key words: Diabetic foot ulcer • Healing Rates • Percent area reduction • Predicting failure to heal

2010 Consensus Panel



2010 Consensus Panel on Treatment

"The panel recognizes the prognostic value of ***50% percent area reduction*** of the wound at ***four weeks*** and recommends utilization of this parameter as a **clinical decision point for the use of advanced therapies** in healing DFUs. Use of advanced modalities, when indicated, should be viewed as the ***new standard of care*** and these advanced modalities should not be a **'last resort'** in the treatment of DFUs."

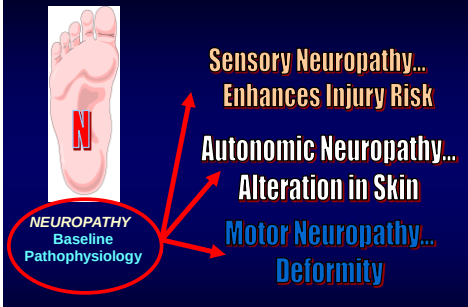
Snyder et al. Ostomy Wound Management. April, 2010 "Consensus Recommendations for Advancing the Standard of Care for Treating Neuropathic Foot Ulcers in Patients with Diabetes."

DFU...Understanding the pathophysiology

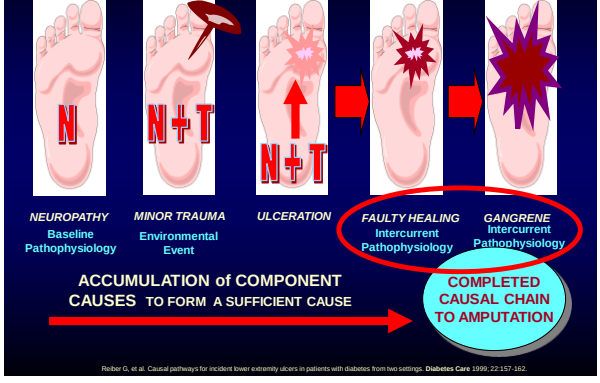
Essential!!!

Pathophysiology of DFU

Account for DFU Pathophysiology

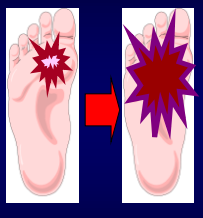


Account for DFU Pathophysiology



Reiber G, et al. Causal pathways for incident lower extremity ulcers in patients with diabetes from two settings. **Diabetes Care** 1999; 22:157-162.

Account for DFU Pathophysiology
Causes of Faulty Healing



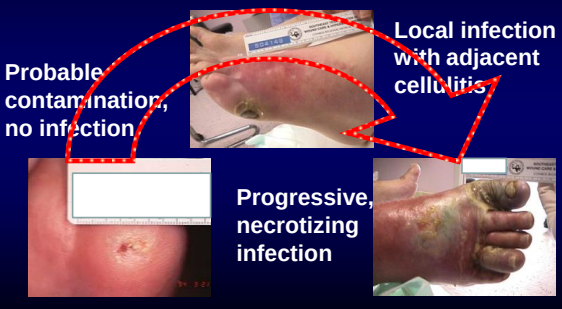
1. Infection
2. Malperfusion/hypoxia
3. Cellular failure
4. Unrelieved pressure
5. Age

Reiber G, et al. Causal pathways for incident lower extremity ulcers in patients with diabetes from two settings. **Diabetes Care** 1999; 22:157-162.

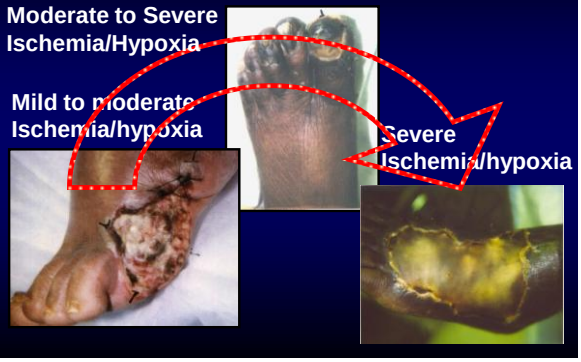
Diabetes Mellitus: Mechanisms of Cellular Failure

- Protein glycation and advanced glycation end products (glycosolated Hgb)
- Accelerated atherosclerosis
- Hyperglycemia
  - Impaired leukocyte function
  - Increased platelet aggregation
- Altered pattern of GF and GF receptor expression
- Impaired collagen synthesis
- Impaired angiogenesis

Account for Spectrum of DFU Presentation



Account for Spectrum of DFU Presentation



DFU…Pathophysiology
Final Common Pathways

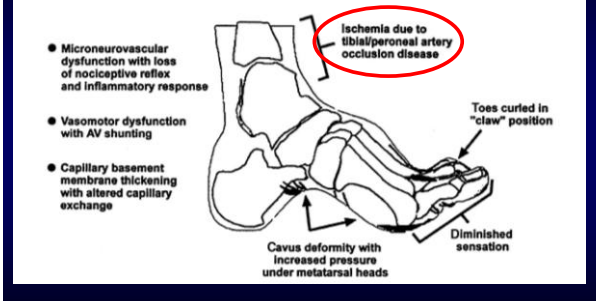
- ❑ Infection
- ❑ Ischemia/hypoxia
- ❑ Cellular failure
- ❑ Pressure/trauma
- ❑ Inflammation

All final common pathways are implicated in DFU healing failure!!

The 2 circulatory systems impacting wound healing…

- **Macrovascular**
  Microcirculation

Macrovascular Arterial Occlusive Disease

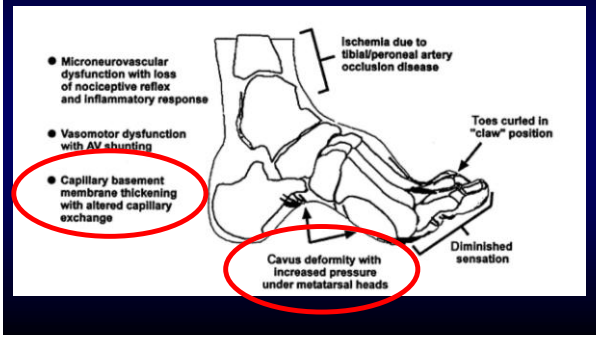


Patterns of Peripheral Arterial Occlusive Disease in Diabetics

- Earlier age of onset
- Characteristic distribution pattern (Strandness, 1964)

	Aortoiliac	Tibial/Peroneal
Non-diabetics	68%	57%
Diabetics	27%	81%

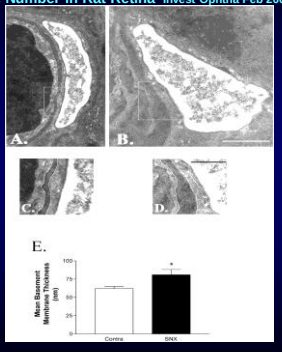
Microvascular Arterial Occlusive Disease



"Small vessel disease" is a misnomer

- Thickening of the basement membrane creates some *inelasticity* and *decrease in capillary size* however this *does not cause narrowing of the capillary lumen*
- Disease is functional rather than obstructive (*Microcirculatory dysfunction* {MD})
- MD may also decrease the movement of leucocytes, thus theoretically making diabetics more susceptible to infection

Sympathetic Innervation Regulates Basement Membrane Thickening and Pericyte Number in Rat Retina Invest Ophtha Feb 2005



Vascular disease in Patients with Diabetes

- Distribution of large vessel disease is different in diabetic patients
- Trifurcation disease with tibial vessel involvement
- The distral vessels are often spared at the level of the ankle(e.g.: PT, AT, Peroneal) making distal bypass and endovascular intervention possible
- Often the goal of an operative intervention is to improve *microcirculatory dysfunction*

Snyder et al. Ostomy Wound Management. April, 2010 "Consensus Recommendations for Advancing the Standard of Care for Treating Neuropathic Foot Ulcers in Patients with Diabetes

Microcirculatory abnormalities not always reversed by correction macrovascular abnormalities…

- J Vasc Surg 2002;35:501-5 Arora et al (LoGerfo) Impaired vasodilation in diabetic neuropathic lower extremities improves but is not completely reversed with successful bypass grafting.(laser doppler trial)
- Post revascularization diabetic patients may still be at risk for foot ulceration and may fail to heal the ulcer despite adequate correction of macrovascular flow

The Angiosome Concept

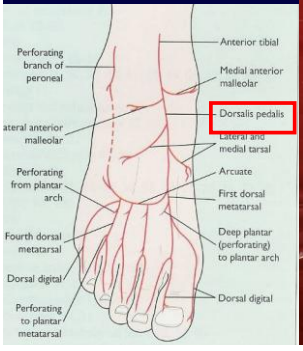
- A new paradigm in evaluating and treating vascular disease in patients with diabetes
- Taylor and Palmer(1987)
- Dr. Chris Attinger: Pioneered the angiosome model in the diabetic foot

Angiosomes in the Diabetic Foot

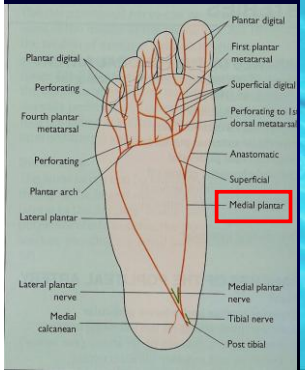
- There are *6 angiosomes* in the foot that originate from the three major arteries in the lower leg (PT, AT/DP, Peroneal)
- *Choke vessels* mark the boundary of any angiosome and can supply blood to an adjacent angiosome through the delay phenomenon
- *Arterial-arterial connections*: Allow uninterrupted blood flow to the entire foot despite the occlusion of one or more arteries (vascular redundancy; vascular rescue)

The distribution of 6 angiosomes in the foot create vascular redundancy. This generates multiple pathways to augment blood supply to an injured/ulcerated area

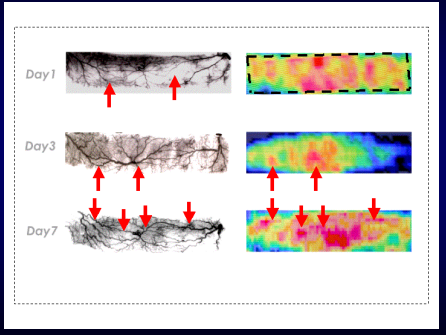
Anterior Tibial to Dorsal Pedal Artery Angiosomes



Medial Plantar Angiosome



Choke vessels in a rat model



Foot ulcers in patients with diabetes can be classified as *neuropathic*, *neuroischemic*, or *ischemic* however there is often an overlap between macro and microvascular disease that "blurs the lines" between these entities.

Neuro-ischemic (foot margins)

Neuropathic (Plantar with callus)

Ischemic (distal)

Wagner Classification Diabetic Foot Ulcers

- **Grade 0:** Intact skin
- **Grade I:** Superficial without penetration deeper layers
- **Grade II:** Deeper reaching tendon, bone, or joint capsule
- **Grade III:** Deeper with abscess, osteomyelitis, or tendonitis extending to those structures
- **Grade IV:** Gangrene of some portion of the toe, toes, and/or forefoot
- **Grade V:** Gangrene involving the whole foot or enough of the foot that no local procedures are possible

Wagner FW. Foot & Ankle 1981, 64-122

Wagner Grade I
Superficial without penetration deeper layers (some portion of dermis intact, no subcutaneous involvement)

Wagner Grade I
Superficial without penetration deeper layers (some portion of dermis intact, no subcutaneous involvement)

Problem with Wagner Grading System…this is anatomically a Wagner I but is infected and clearly has a different risk presentation than the previous example.

Wagner Grade II
Full thickness reaching tendon, bone, or joint capsule without infection of ischemia

What about "probe to bone"?

Wagner Grade III
Full thickness with abscess, osteomyelitis, or tendonitis (any infection) extending to those structures

Wagner Classification Diabetic Foot Ulcers

- Grade 0: Intact skin
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- Grade V: Gangrene involving the whole foot or enough of the foot that no local procedures are possible

Grade I & II w/Infection = Grade III

Wagner FW. Foot & Ankle 1981, 64-122

Wagner Grade IV

Gangrene of some portion of the toe, toes, and/or forefoot

Wagner Grade V

Gangrene involving the whole foot or enough of the foot that no local procedures are possible

Grade/depth: "How deep is the wound?"					
		0	I	II	III
Stage/ Comorbidities: "Is the wound infected, ischemic, or both?"	A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
	B	Pre- or post-ulcerative lesion completely epithelialized with infection	Superficial wound not involving tendon, capsule or bone with infection	Wound penetrating to tendon or capsule with infection	Wound penetrating to bone or joint with infection
	C	Pre- or post-ulcerative lesion completely epithelialized with ischemia	Superficial wound not involving tendon, capsule or bone with ischemia	Wound penetrating to tendon or capsule with ischemia	Wound penetrating to bone or joint with ischemia
	D	Pre- or post-ulcerative lesion completely epithelialized with infection and ischemia	Superficial wound not involving tendon, capsule or bone with infection and ischemia	Wound penetrating to tendon or capsule with infection and ischemia	Wound penetrating to bone or joint with infection and ischemia

11X greater risk mid foot or higher amp

90X greater risk mid foot or higher amp

Figure 1. University of Texas Classification System for Diabetic Foot Wounds. (From: Armstrong, DG, Lavery, LA, Harkless, LB. Diabetes Care 1998; 21: 855-859, Lavery, LA, Armstrong, DG, Harkless, LB. J Foot Ankle Surg. 1996; 35:528-531).

Evaluation and Classification

Foot and Ulcer Evaluation

- Initial event and wound heali be considered
- Foot ulcer examination shoul
  - Dermatological changes
  - Ulcer characteristics, dimensio
  - Probe Test
  - Presence of Necrosis and wou

Wound Classification

- The University of Texas syste matrix of grades is recomme
- The Wagner System may be r reimbursement

DFU… Critical Principles

- ***ALL*** **patients with a neuropathic diabetic foot ulcer should be assessed for arterial disease with revascularization (endovascular or surgical) completed when indicated.**

DFU…Assessment

Clinically significant arterial disease should be excluded in all patients that pe… the… additio…

The presence of pedal pulses does not preclude significant vascular disease

DFU… Critical Principles

- Effective offloading should be achieved using total contact casting or removable orthotic walkers affixed in such a way as to prevent removal.

DFU…Offloading

Ensure adequate offloading of pressure through wound closure. A… …of therapeutic offloadi… …tiveness (Le…

- …
- …prev… …)
- Post operative shoes, felt and foam dressings with crutch walking or use of walker in Wagner grade I ulcers

Often it is not what you put on the wound but what you take off the wound that facilitates healing

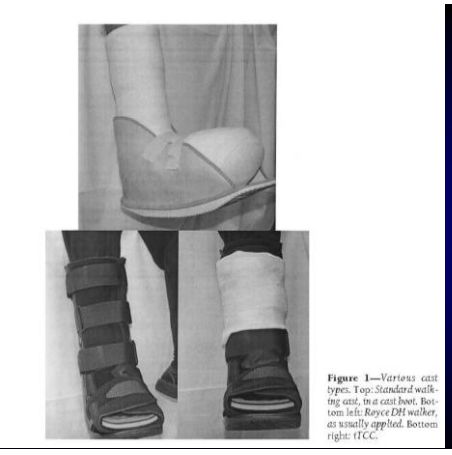
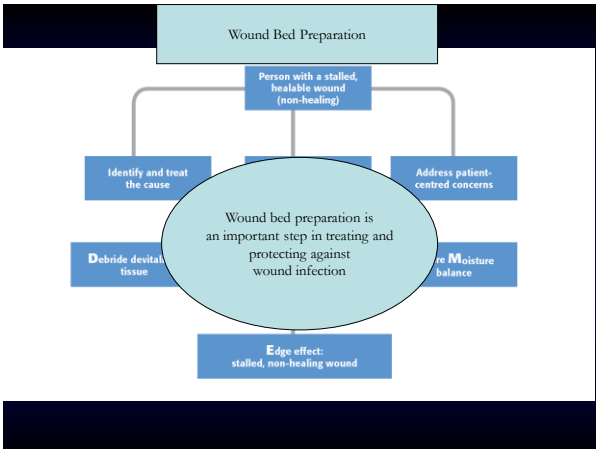


Figure 1—Various cast types. Top: Standard walking cast, in a cast boot. Bottom left: Royce DH walker, as usually applied. Bottom right: TCC.

DFU… Critical Principles

- **Early closure** is the single most impor… …vent…

Debridement plays a critical role



Indications for Debridement in DFU Care

- **Presence of callous**
- **Presence of undermining of ulcer edges (margination of keratinocytes)**
- **Presence of necrotic tissue in the wound bed**

Saap LJ, Falanga V. Wound Rep Reg 2002; 10:354-359.

- **Remove biofilm, debrided osteo**

Surgical Planning

- The importance of blood flow and oxygen delivery to a wound bed cannot be overstated
- Despite heroic efforts by wound care specialists, ulcerations will not heal in the presence of pronounced peripheral vascular disease
- Vascularity, therefore, remains of prime importance when evaluating a patient for an operative intervention.

Ennis WJ, Menseze P (2002) Factors impeding wound healing. In: L. Kloth and J. McCulloch (eds.) *Wound Healing: Alternatives in Management* Philadelphia: FA Davis Company

Palpable Pedal Pulses

- **There is no single noninvasive parameter that will reliably predict healing**
- A palpable pulse does not always indicate appropriate vascularity
- **It therefore, remains imperative to have vascular and endovascular consultation**

Bloomgarden ZT (2005) Diabetic retinopathy and neuropathy. *Diabetes Care.* 28 (4) 963-970
Snyder R (2007) Controversies regarding vascular disease in the patient with diabetes: a review of the literature. Ostomy Wound Management. 53(11): 26-34

Classification of the Surgical Patient

- **Surgical patients may be classified as** emergent, elective, or palliative
- **In the two latter scenarios, vascular work-up and intervention when necessary should be performed** before **surgery commences**
- However, emergent cases often require life and limb saving intervention before vascular issues are addressed.

Example of Emergent Surgical Intervention

2010 Consensus Panel on Treatment

"The panel recognizes the prognostic value of ***50% percent area reduction*** of the wound at ***four weeks*** and recommends utilization of this parameter as a **clinical decision point for the use of advanced therapies** in healing DFUs. Use of advanced modalities, when indicated, should be viewed as the ***new standard of care*** and these advanced modalities should not be a **'last resort'** in the treatment of DFUs."

Snyder et al. Ostomy Wound Management. April, 2010 "Consensus Recommendations for Advancing the Standard of Care for Treating Neuropathic Foot Ulcers in Patients with Diabetes."

GROUP ONE: The Ideal Patients
Clinical Targets: The Stalling Ulcer
(4 Weeks < 50% Progress)



GROUP TWO: The Ideal Patients
Clinical Targets: Ulcers that are doing
"good" or "ok (4 Weeks < 50% Progress)

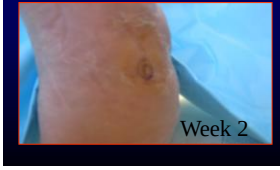





- Clinical Case Studies

Clinical Case Studies

HFDS With Total Contact Cast



Clinical Case Studies

Rapid Wound Closure NPWT & HSE 5 weeks



Dehisced Surgical Wound

- 68 year-old male with IDDM
- H/O osteomyelitis and ischemia
- Treated with multiple angioplasties and stents; bypass to plantar arch
- Multiple wound and bone debridements culminating in a Transmetatarsal amputation utilizing part of the great toe as the flap / percutaneous TAL
- Wound became dusky and dehiscence observed
- H/O heart disease, hypertension, PVD, generalized arthritis, renal insufficiency

Dehisced Wound

Neuropathic ulcer with bone exposed

- 78 year-old male with diabetes presented with decubitus heel ulcer of 1 month duration
- Diabetes liable; IDDM
- Non-palpable pedal pulses, foot cool, capillary refill delayed
- Semmes-Weinstein greater than 5.07
- Non-ambulatory; no pacemaker
- H/O heart disease, hypertension, dyslipidemia, and renal insufficiency requiring dialysis

Patient had angioplasty, then underwent wound and bone debridement. A cadaveric allograft was applied and NPWT was instituted. Infection was treated with antibiotics.

Wound Bed Preparation and sequential/ combination therapy create significant clinical improvement.
This represents a perfect scenario for the use of serial applications of an advanced therapy

- 67 year old male with IDDM
- H/O blockage of posterior tibial opened with angioplasty
- Burned his foot with a heating pad
- Severe neuropathy
- Presented to the office with an infection requiring hospitalization

Negative Pressure Wound Therapy in conjunction with several human skin equivalents applied weekly, HBO
Split-Thickness Skin Grafts were ultimately utilized for complete closure



- Ulceration in Male with Diabetes, PVD and Neuropathy
- H/O BKA contralateral limb
- H/o remote MI, renal insufficiency, hypertension, dyslipidemia
- Non-palpable pedal pulses, foot cool, capillary refill delayed
- Semmes-Weinstein greater than 5.07

S/P angioplasty and extensive wound debridement. IV antibiotics and PMMA beads were used. NPWT therapy and HBO started


Serial human skin substitutes utilized;
NPWT therapy and HBO continued through placement of split-thickness skin graft


- Wound size was 18.75 cm2
- Application of EpiFix® Graft with **30%** area reduction at ***7 days***
- Additional **15%** area reduction at ***Day 14***
- Additional application of EpiFix® Graft and ***wound closed at day 28***
- At 3 months wound remains fully closed and patient walking with custom molded shoe

Abscessed foot in a neuropathic patient with diabetes: a stepwise approach

What we are trying to prevent!

At the end of the day

Its all about the patient